LUNG CANCER UPDATES
ASCO HIGHLIGHTS
1-5 JUNIO 2018, CHICAGO

# NSCLC estage IV. inmunoterapia

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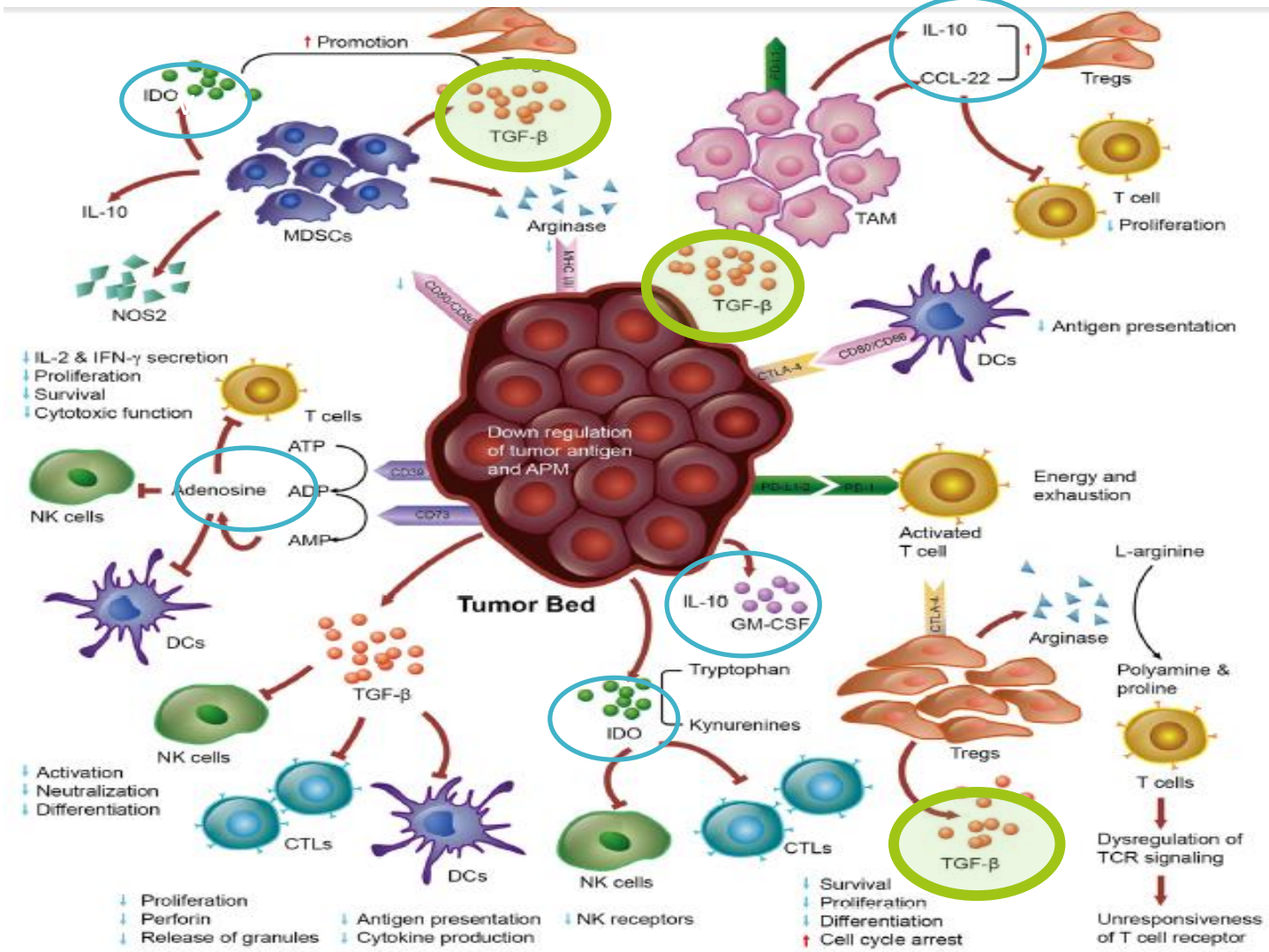
# 2º line stage IV NSCLC. Treatment with inmunotherapy


↑ Promotion
IDO
TGF-β
IL-10
MDSCs
Arginase
NOS2
PD-L1
IL-10
CCL-22
Tregs
T cell
↓ Proliferation
TAM
TGF-β
↓ Antigen presentation
DCs
CD80/CD86
CTLA-4
↓ IL-2 & IFN-γ secretion
↓ Proliferation
↓ Survival
↓ Cytotoxic function
T cells
ATP
ADP
AMP
Adenosine
NK cells
CD39
CD73
Down regulation of tumor antigen and APM
PD-L1/2
PD-1
Energy and exhaustion
Activated T cell
DCs
Tumor Bed
IL-10
GM-CSF
L-arginine
CTLA-4
Arginase
Polyamine & proline
TGF-β
Tryptophan
IDO
Kynurenines
Tregs
T cells
NK cells
↓ Activation
↓ Neutralization
↓ Differentiation
CTLs
DCs
NK cells
CTLs
TGF-β
Dysregulation of TCR signaling
Unresponsiveness of T cell receptor
↓ Proliferation
↓ Perforin
↓ Release of granules
↓ Antigen presentation
↓ Cytokine production
↓ NK receptors
↓ Survival
↓ Proliferation
↓ Differentiation
↑ Cell cycle arrest

# Results from a second-line (2L) NSCLC cohort treated with M7824 (MSB0011359C), a bifunctional fusion protein targeting TGF-β and PD-L1.



- Inhibiting the transforming growth factor β (TGF-β) pathway, which promotes tumor immunosuppression, may enhance the response to PD-(L)1 monoclonal antibodies (mAbs).
- Expansion cohort of phase 1 trial NCT02517398 progressed following 1L standard treatment .
- **Randomized to receive M7824 500 mg (n = 40) or 1200 mg (n = 40) q2w . 80 pts.**
- The primary objective is to assess BOR per RECIST v1.1; dose exploration and safety/tolerability assessment.
- Tumor cell PD-L1 expression was evaluable in 75 pts (Ab clone 73-10 [ > 80% = > 50% with 22C3]).
- **Results**: Investigator-assessed **unconfirmed ORR was 25.0%** (500 mg ORR, 22.5%; 1200 mg ORR, 27.5%). **ORR was 40.7% in PD-L1+ and 71.4% in PD-L1–high pts at 1200 mg.**
- Adverse events (TRAEs) were pruritus (18.8%), maculopapular rash (17.5%), and decreased appetite (12.5%). **Grade ≥3 TRAEs occurred in 20 pts** (25.0%). 6 pts (500 mg, n = 2; 1200 mg, n = 4) discontinued treatment due to TRAEs. No treatment-related deaths occurred.
- Conclusions: M7824 monotherapy had promising efficacy across PD-L1 subgroups, with an ORR at the RP2D of 1200 mg of 40.7% and 71.4% in PD-L1+ and –high pts, respectively. Treatment was well tolerated.

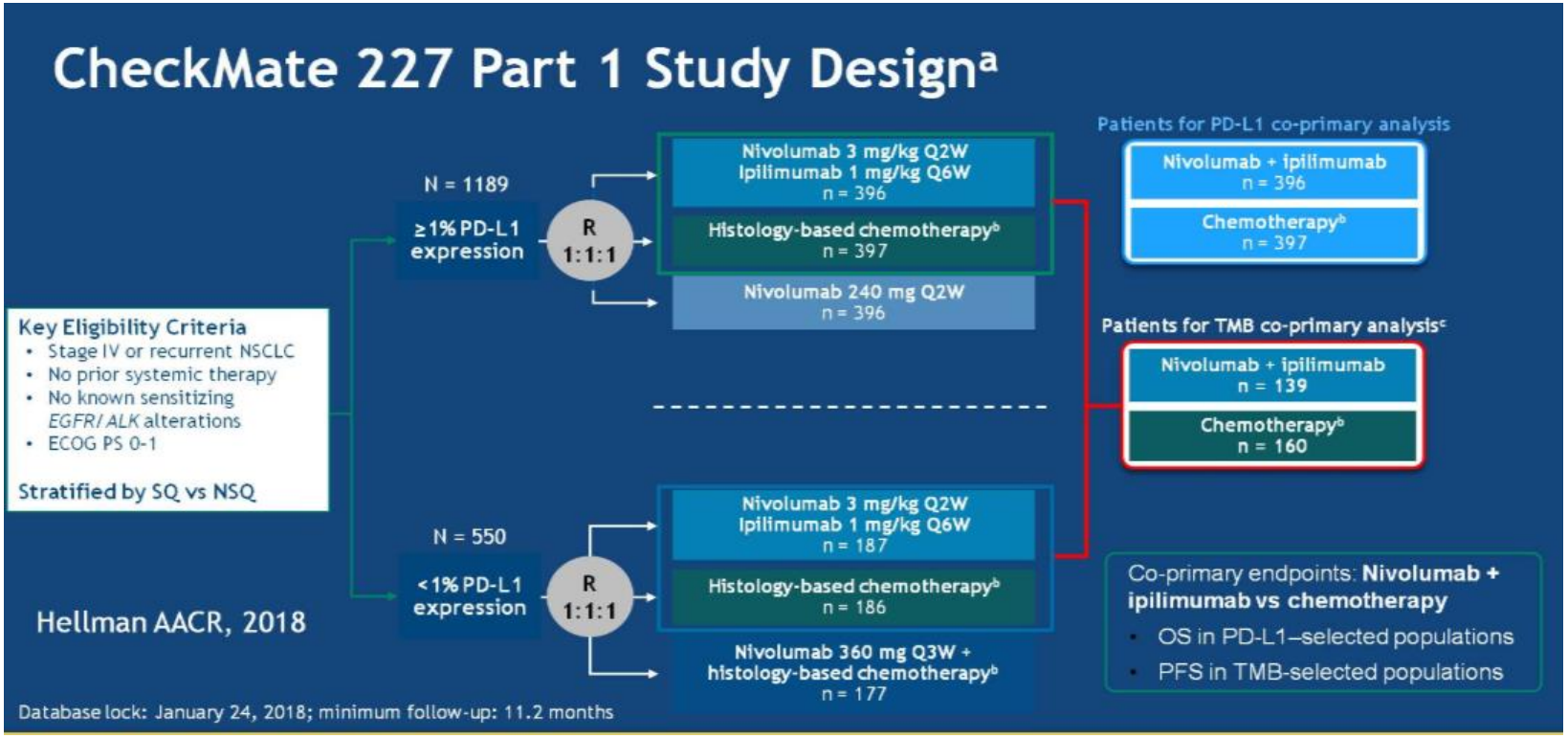
| ORR | 500 mg | 1200 mg | Total |
|---|---|---|---|
| All | 9/40, 22.5 | 11/40, 27.5 | 20/80, 25.0 |
| PD-L1+ (≥1%) pts, n, % | 7/31, 22.6 | 11/27, 40.7 | 18/58, 31.0 |
| PD-L1 high (≥80%) pts, n, % | 2/6,33.3 | 5/7,71.4 | 7/13,53.8 |

*Luis G. Paz-Ares. ASCO 2018 .Poster discussion. Abstract #: 9017*


# 1º line stage IV NSCLC. Treatment with inmunotherapy

# Nivolumab (Nivo) + Ipilimumab (Ipi) vs Platinum-Doublet Chemotherapy (Chemo) as First-line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Safety Analysis and Patient-Reported Outcomes (PROs) From CheckMate 227

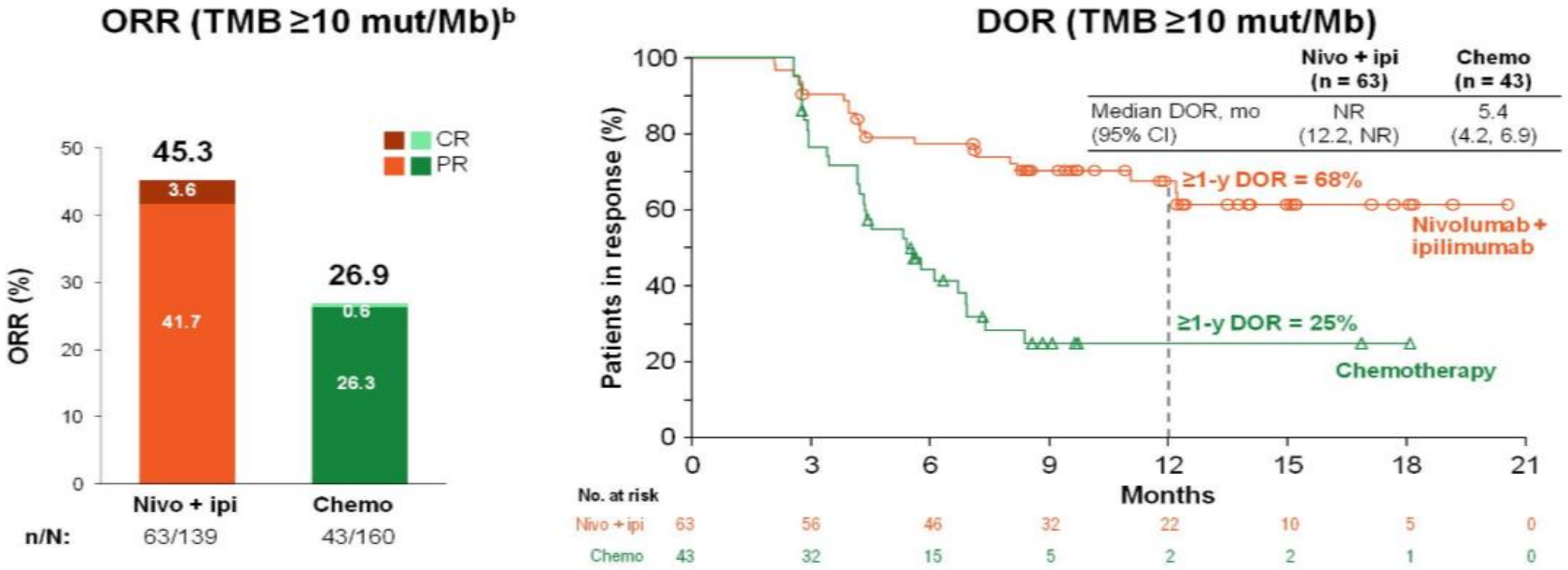





**CheckMate 227 (NCT02477826) is a phase 3 study of 1L nivo + ipi, nivo, or nivo + chemo vs chemo in advanced NSCLC with different levels PD-L1 expresion. randomized 1:1:1 to nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W), nivo monotherapy (240 mg Q2W), or chemo for pts with ≥1% tumor PD-L1 expression and to nivo + ipi, nivo (360 mg Q3W) + chemo, or chemo for pts with < 1% tumor PD-L1.**

*Reck, M. ASCO 2018. Poster discusion. Abstract #:9020*

# ORR and DOR in Patients With High TMB (≥10 mut/Mb)[a]




- Median time to response was 2.7 months with nivolumab + ipilimumab and 1.5 months with chemotherapy

Hellman AACR, 2018

[a] Per BICR; [b] ORR in patients with TMB <10 mut/Mb was 24.6% in nivo + ipi arm and 25.9% in chemo arm

The study met its co-primary endpoint demonstrating significantly prolonged PFS with nivo + ipi vs chemo in patients (pts) with tumor mutational burden ≥10 mutations/Mb.

*Reck, M. ASCO 2018. Poster discusion*

- Median duration of therapy was 4.2 mo with nivo + ipi and 2.6 mo with chemo. Rates of **any grade** and **grade 3–4 TRAEs** were **75%** and **31%** with **nivo + ipi**, and **81%** and **36%** with **chemo**, respectively.

- **TRAEs led to discontinuation** in **17%** of pts receiving **nivo + ipi** and in **9%** of pts receiving **chemo**. Most frequent **grade 3–4 select TRAEs** in pts receiving **nivo + ipi** were hepatic (8%), endocrine (4%), skin (4%), pulmonary (3%), and gastrointestinal (2%).

- **Median time to onset** of select TRAEs ranged **from 2–15 wk**, and the majority resolved with corticosteroid use (**median time to resolution was ≤10 wk**).

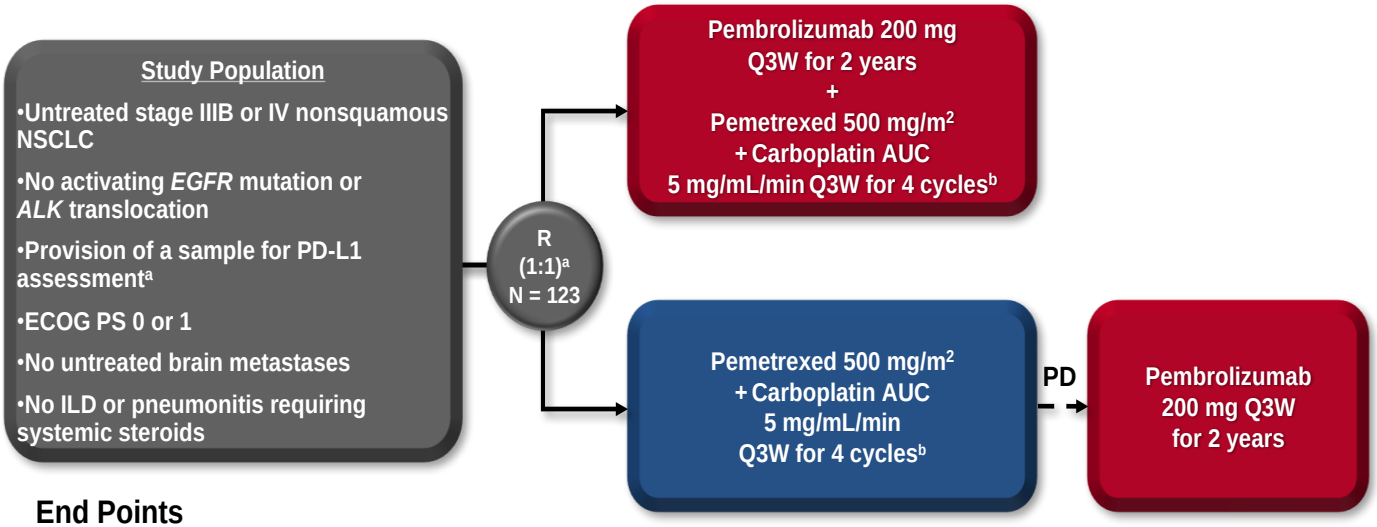
- **Conclusions:**In CheckMate 227, nivo + low-dose ipi was well tolerated in NSCLC.

*Reck, M. ASCO 2018. Poster discusion*

# 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC.



## KEYNOTE-021 Cohort G




**End Points**

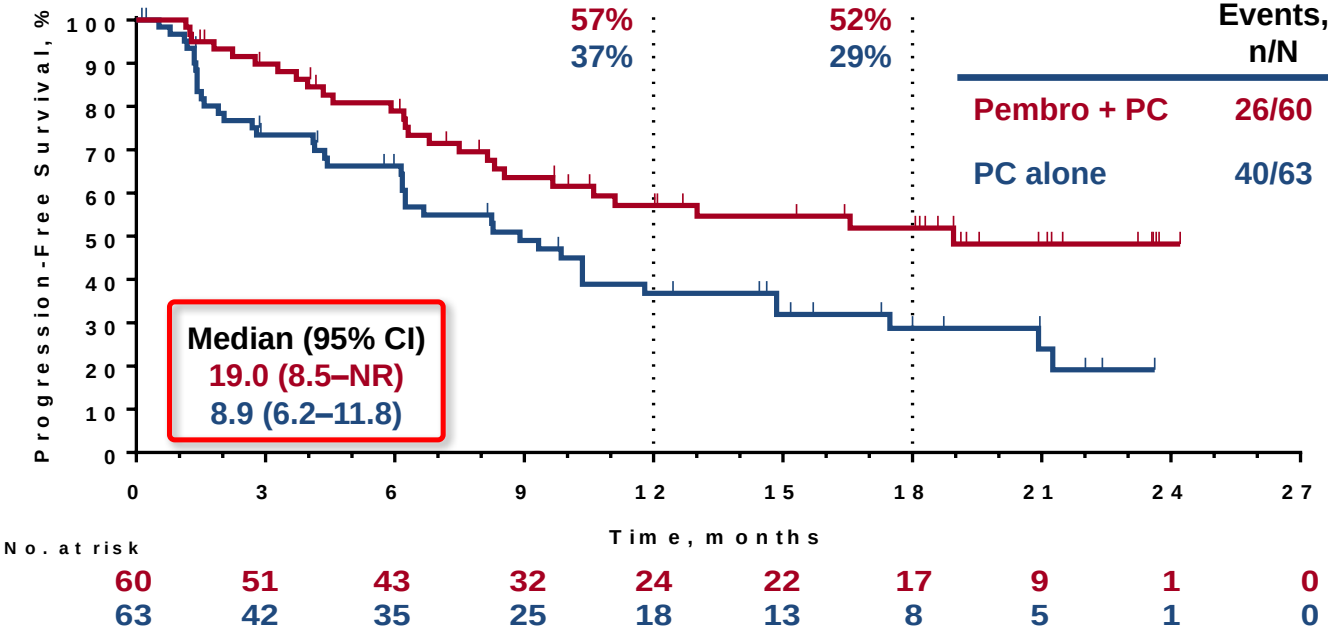
- Primary: ORR (RECIST v1.1 per blinded, independent central review)
- Key secondary: PFS
- Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS
- No alpha allocated for updated analysis; all *P* values are nominal (one-sided $P < 0.025$)

PD, progressive disease.
[a]Randomization was stratified by PD-L1 TPS <1% vs ≥1%. [b]Indefinite maintenance therapy with pemetrexed 500 mg/m2 Q3W permitted.

Cohort G of the phase 1/2 KEYNOTE-021 study (NCT02039674) evaluated pembrolizumab (pembro) + pemetrexed and carboplatin (PC) vs PC in first-line advanced nonsquamous NSCLC

*Ryan D. Gentzler. . ASCO 2018. Poster dicusion.*

# Progression-Free Survival
## (RECIST v1.1 by Blinded, Independent Central Review)




| | Events, n/N | HR (95% CI) |
|---|---|---|
| Pembro + PC | 26/60 | 0.54 (0.33–0.88) |
| PC alone | 40/63 | *P* = 0.0067[a] |

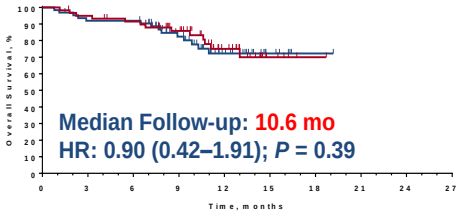
[a]P value is descriptive (one-sided P < 0.025).
Data cut-off: May 31, 2017.

With median follow-up of 10.6 mo, ORR (estimated treatment difference, 26%; *P* = 0.0016) and PFS (HR, 0.53; *P* = 0.010) significantly improved with pembro + PC vs PC. The HR for OS was 0.90 (95% CI, 0.42–1.91).

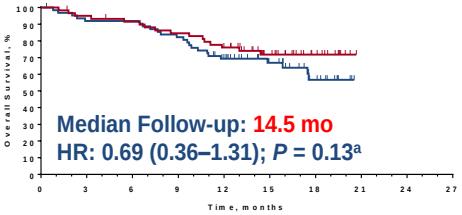
*Ryan D. Gentzler. . ASCO 2018. Poster dicusion.*

# Overall Survival

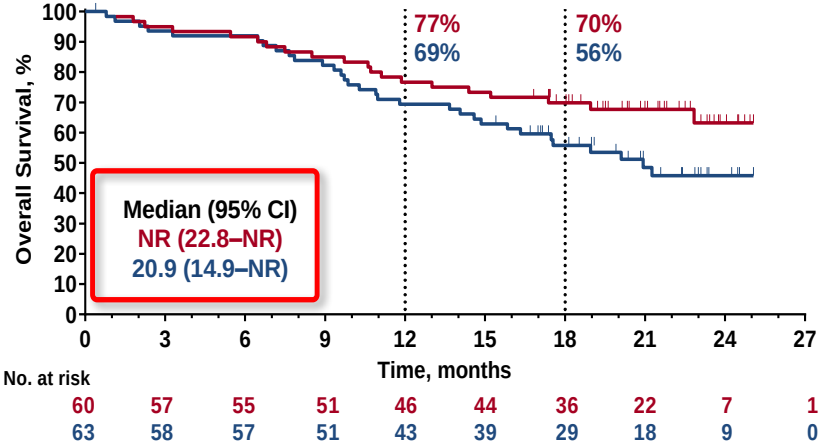
## Data Cut-off: August 8, 2016[1]




## Data Cut-off: December 31, 2016[2]




## Data Cut-off: May 31, 2017




Median Follow-Up: 18.7 mo

| | Events, n/N | HR (95% CI) |
|---|---|---|
| Pembro + PC | 20/60[b] | 0.59 (0.34–1.05) |
| PC alone | 31/63[b] | P = 0.03[a] |

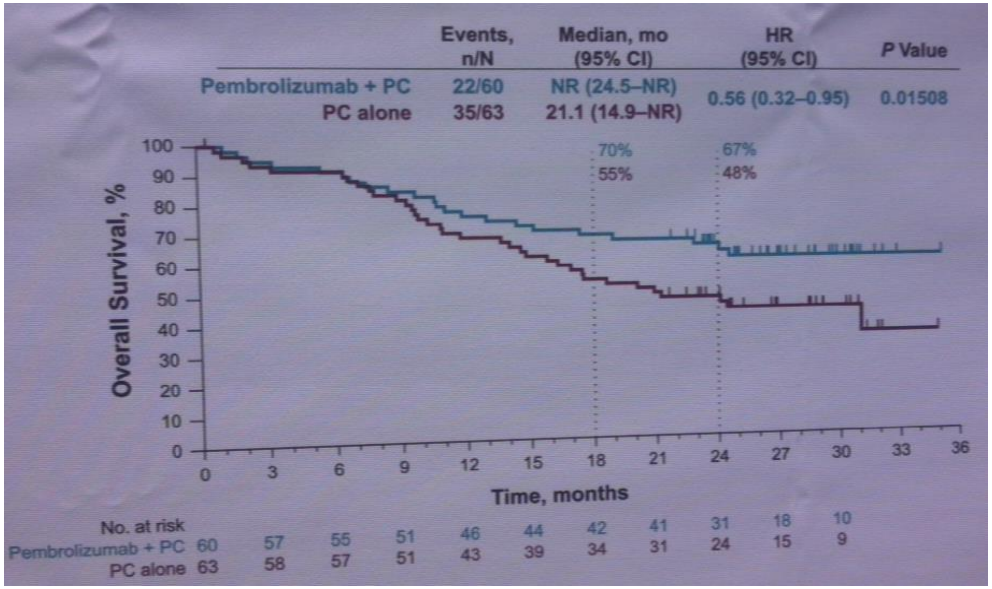
1. Langer CJ, et al. Lancet Oncol. 2016;17(11):1497-1508. 2. Papadimitrakopoulou VA, et al. 2017. J Clin Oncol. 35(suppl): abstract 9094.
[a]P value is descriptive (one-sided P < 0.025). [b]24 additional deaths since primary analysis (pembro + PC, n = 7; PC alone, n = 17).

*Ryan D. Gentzler. . ASCO 2018. Poster dicusion.*

# 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC.



- **Results:** 123 pts were randomized. As of **Dec 1, 2017, median follow up was 23.9 mo (range, 0.8–35.1 mo**
- ORR was 57% with pembro + PC vs 30% with PC (*P* = 0.0016).
- PFS was significantly improved with pembro + PC vs PC (HR, 0.53; 95% CI, 0.33–0.86; *P* = 0.0049). Median (95% CI) PFS was 24.0 (8.5–NR) mo for pembro + PC vs 9.3 (6.2–14.9) mo for PC.
- **HR for OS was 0.56** (95% CI, 0.32–0.95; *P* = 0.0151). Median (95% CI) OS was not reached (24.5 mo–NR) for pembro + PC and 21.1 (14.9–NR) mo for PC; **24-mo OS rates were 67% and 48%.**
- **Conclusions:** After median follow-up of approximately 24 mo, the risk of death for pembro + PC vs PC was reduced by nearly half (HR, 0.56; nominal *P* = 0.0151) despite a high crossover rate among patients in the PC arm.

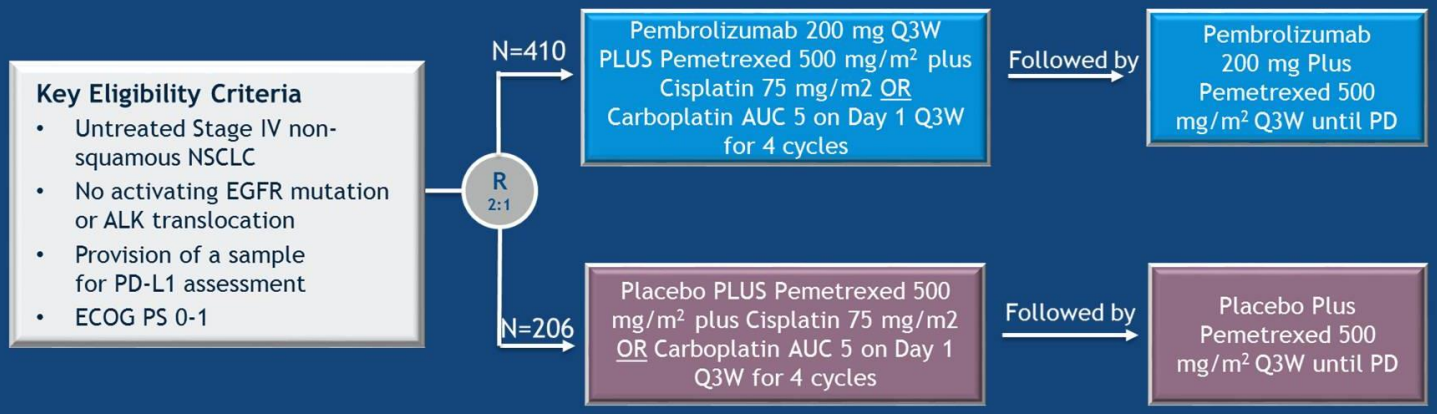



*Ryan D. Gentzler. . ASCO 2018. Poster dicusion.*

# Health-related quality of life (HRQoL) in the KEYNOTE-189 study of pembrolizumab (pembro) or placebo (pbo) + pemetrexed (pem) + platinum (plt) for metastatic NSCLC.



## KEYNOTE 189: Randomized, Double-Blind, Phase III Study of Platinum+Pemetrexed Chemotherapy With or Without Pembrolizumab in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects




**Stratification Factors:**
- PDL1 expression (TPS <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

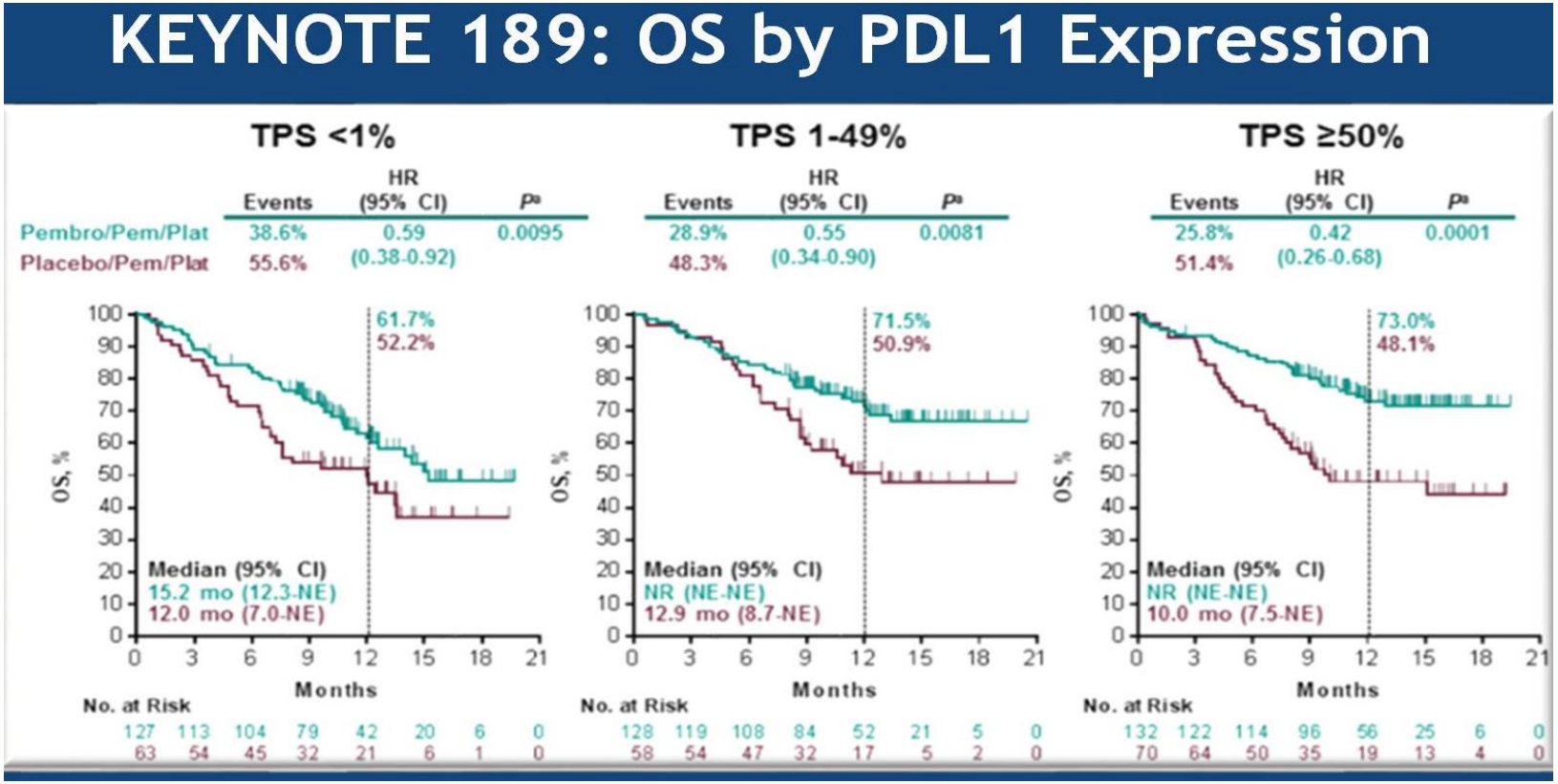
| Frequency of PDL1 TPS | <1% | 1-49% | ≥50% | NE |
|---|---|---|---|---|
| Pembro/Chemo | 31 | 31.2 | 32.2 | 5.6 |
| Chemo | 30.6 | 28.2 | 34 | 7.3 |

In the double-blind, phase 3 KEYNOTE-189 study (NCT02578680), **:** 616 patients (pts) were randomized to pembro 200 mg Q3W or pbo for 2 y; all pts received pem + 4 cycles of carboplatin or cisplatin.

*Marina Chiara Garassino. ASCO 2018. Poster dicusion. Abstract 9021*

# Health-related quality of life (HRQoL) in the KEYNOTE-189 study of pembrolizumab (pembro) or placebo (pbo) + pemetrexed (pem) + platinum (plt) for metastatic NSCLC.





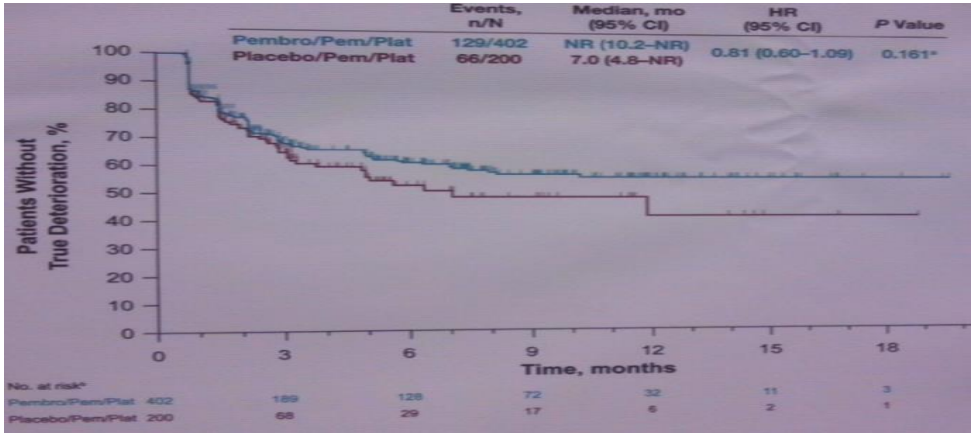

Pembro + pem + plt significantly improved OS and PFS over pbo + pem + plt as first-line therapy for nonsquamous NSCLC. Independent of PD-L1 expression

*Marina Chiara Garassino. ASCO 2018. Poster dicusion.*

# Health-related quality of life (HRQoL) in the KEYNOTE-189 study of pembrolizumab (pembro) or placebo (pbo) + pemetrexed (pem) + platinum (plt) for metastatic NSCLC.



- Grade 3-5 drug-related AE rates were higher with pembro.
- The EORTC QLQ-C30 and QLQ-LC13 were administered at cycles 1-5, then every 3 cycles during yr 1 and every 4 cycles during yrs 2 and 3.
- Key PRO outcomes were change from baseline to wks 12 and 21 in the QLQ-C30 global
- QLQ-C30 and QLQ-LC13 compliance was ~90% at baseline and wk 12 in both arms and was ~75% with pembro and ~63% with pbo at wk 21.
- At wks 12 and 21, **global health status/QoL scores** were **stable with pembro** and **decreased with pbo**, with significantly greater decrement with pbo at wk 21 (Table).
- The proportion of **improved global health status/QoL was greater with pembro at wk 21 (30.1% vs 22.5%; *P* = .0496)**. **Median time to deterioration** in the composite of ***cough, chest pain, or dyspnea*** was **NR with pembro** (95% CI 10.2 mo-NR) vs **7.0 mo** (95% CI, 4.8-NR) **with pbo** (HR 0.81; 95% CI 0.60-1.09; nominal 2-sided *P* = .081).
- **Conclusions:** pembro + pem + plt maintained or improved HRQoL over pem + plt alone despite a higher grade 3-5 treatment-related AE rate




*Marina Chiara Garassino. ASCO 2018. Poster dicusion.*

# KEYNOTE: Phase 3 Study of Carboplatin-Paclitaxel/Nab-Paclitaxel With or Without Pembrolizumab for Metastatic Squamous NSCLC



Paz-Ares KN407 ASCO 2018

## KEYNOTE-407 Study Design (NCT02775435)

**Key Eligibility Criteria**
- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

R (1:1)

Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Pembrolizumab 200 mg Q3W for up to 31 cycles

Placebo (normal saline) Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk) → Placebo (normal saline) Q3W for up to 31 cycles

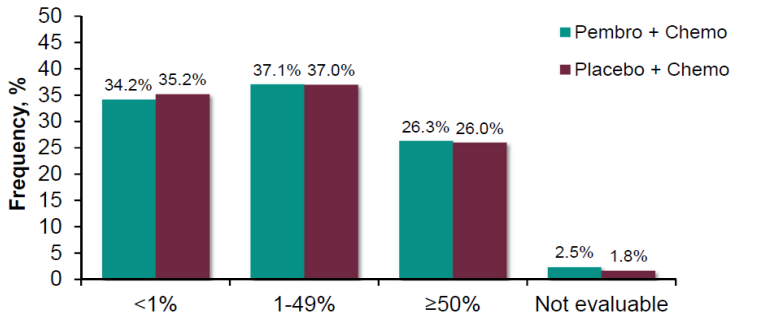
**Stratification Factors**
- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

**End points**
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35 cycles ← PD[b]

BICR, blinded independent central radiologic review. [a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

## Frequency of PD-L1 TPS Categories



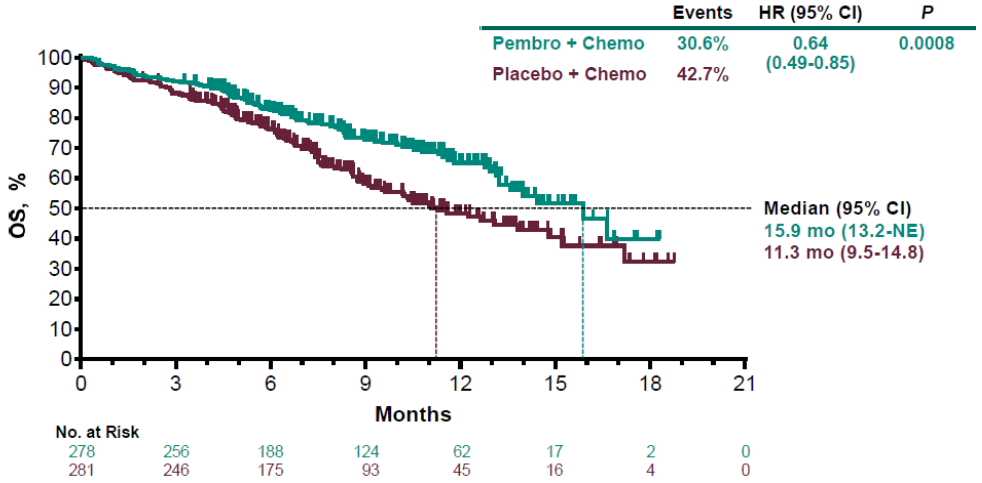

Not evaluable refers to specimens with an inadequate number of tumor cells or no tumor cells seen; these patients were included in the PD-L1 TPS <1% group for randomization stratification but excluded from analyses of efficacy by TPS. Data cutoff date: Apr 3, 2018.

*Luis Paz-Ares. ASCO 2018. ORAL*

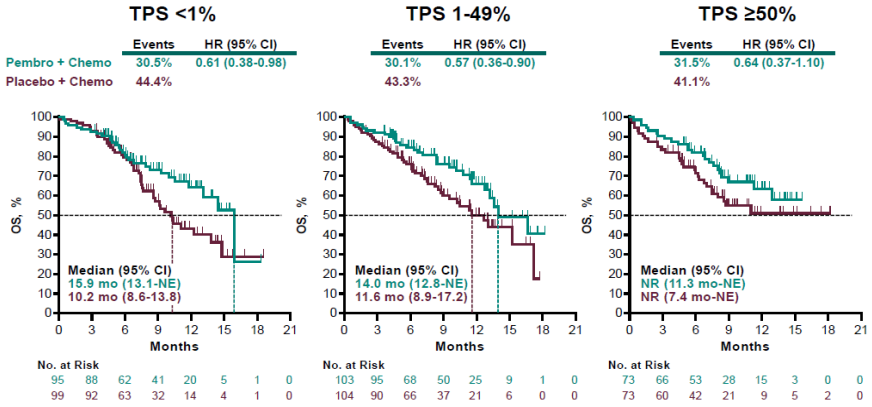
# KEYNOTE: Phase 3 Study of Carboplatin-Paclitaxel/Nab-Paclitaxel With or Without Pembrolizumab for Metastatic Squamous NSCLC



## Overall Survival at IA2, ITT




## Overall Survival at IA2 by PD-L1 TPS




*Luis Paz-Ares. ASCO 2018. ORAL*

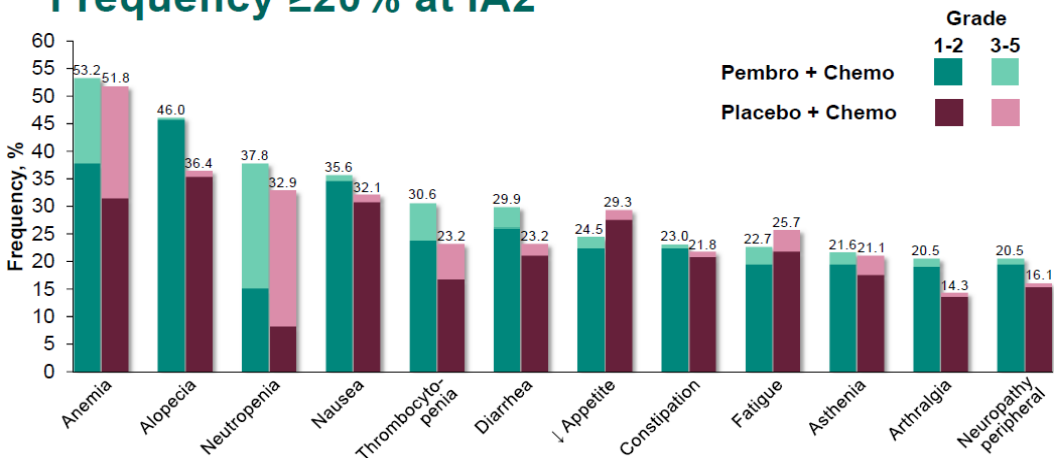
# KEYNOTE: Phase 3 Study of Carboplatin-Paclitaxel/Nab-Paclitaxel With or Without Pembrolizumab for Metastatic Squamous NSCLC



## Summary of Adverse Events at IA2

| | Pembro + Chemo N = 278 | Placebo + Chemo N = 280 |
|---|---|---|
| All cause AEs | 273 (98.2%) | 274 (97.9%) |
| Grade 3-5 | 194 (69.8%) | 191 (68.2%) |
| Led to death | 23 (8.3%) | 18 (6.4%) |
| Treatment-related | 10 (3.6%) | 6 (2.1%) |
| Led to discontinuation | | |
| All treatment[a] | 37 (13.3%) | 18 (6.4%) |
| Any treatment | 65 (23.4%) | 33 (11.8%) |
| Immune mediated AEs and infusion reactions | 80 (28.8%) | 24 (8.6%) |
| Grade 3-5 | 30 (10.8%) | 9 (3.2%) |
| Led to death[b] | 1 (0.4%) | 1 (0.4%) |

## Adverse Events (All Cause): Frequency ≥20% at IA2




*Luis Paz-Ares. ASCO 2018. ORAL*

# 4-year overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from KEYNOTE-001.

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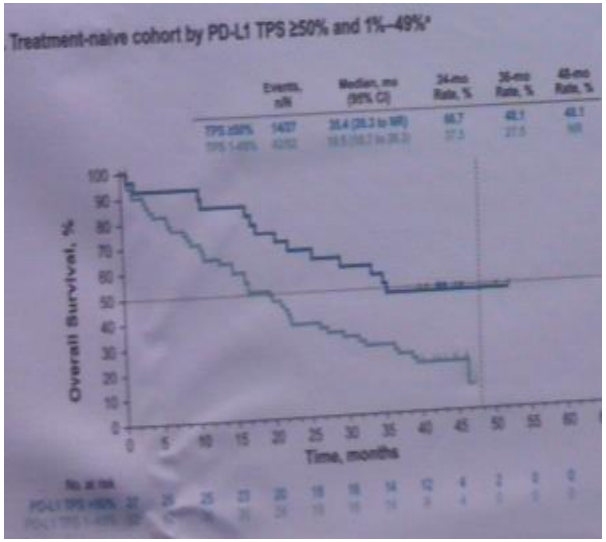
ASCO HIGHLIGHTS
1-5 JUNIO 2018, CHICAGO

- KEYNOTE-001, an open-label phase 1b study, evaluated pembro monotherapy in treatment-naive or previously treated pts with advanced NSCLC (NCT01295827).
- In this study are reported a 4-y
- 550 pts enrolled (treatment-naive, n = 101; previously treated, n = 449), median (range) follow-up was 46.5 (37.7–63.8) mo.
- **Median OS was 22.3 mo (95% CI, 17.1–32.3) for treatment-naive pts** and 10.5 mo (95% CI, 8.6–13.2) for previously treated pts.
- Kaplan-Meier curves for OS appeared to plateau after 42 mo for treatment-naive pts and 36 mo for previously treated pts. Increased PD-L1 expression was associated with improved OS
- **52 pts Treatment-naive, PD-L1 1-49%: median OS: 19.5 months**
- **Conclusions:** Pembro provides long-term OS benefit for both treatment-naive and previously treated advanced NSCLC that expresses PD-L1.




| | Treatment-Naive (N = 101) | | | Previously Treated (N = 449) | | |
|---|---|---|---|---|---|---|
| | n | Median (95% CI), mo | Est. 4-y rate | n | Median (95% CI), mo | Est. 4-y rate |
| TPS ≥50% | 27 | 35.4 (20.3–NE) | 48.1% | 138 | 15.4 (10.6–18.8) | 24.8% |
| TPS 1%–49% | 52 | 19.5 (10.7–26.3) | NE | 168 | 8.5 (6.0–12.6) | 15.6% |
| TPS ≤1% | | Not reported* | | 90 | 8.6 (5.5–10.6) | 6.5% |

*Enriqueta Felip. ASCP 2018.. poster*

GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

# Pembrolizumab versus platinum-based chemoherapy as first line therapy for advanced NSCLC with PD-L1 tumor proportion score (TPS) > 1%: Open label phase III Keynote-042 study



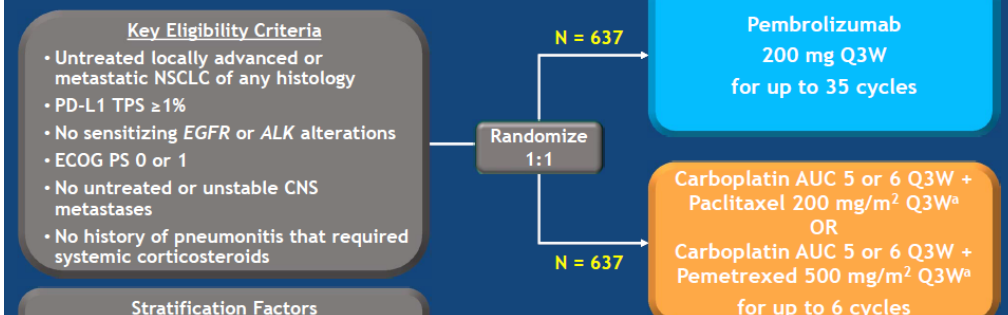
Lopes KN042 ASCO 2018

## Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced/Metastatic NSCLC With a PD-L1 TPS ≥1%: Open-Label, Phase 3 KEYNOTE-042 Study

Gilberto Lopes,[1] Yi-Long Wu,[2] Iveta Kudaba,[3] Dariusz M Kowalski,[4] Byoung Chul Cho,[5] Hande Z Turna,[6] Gilberto Castro, Jr,[7] Vichien Srimuninnimit,[8] Konstantin K. Laktionov,[9] Igor Bondarenko,[10] Karou Kubota,[11] Gregory M Lubiniecki,[12] Jin Zhang,[12] Debra Kush,[12] Tony Mok[13]

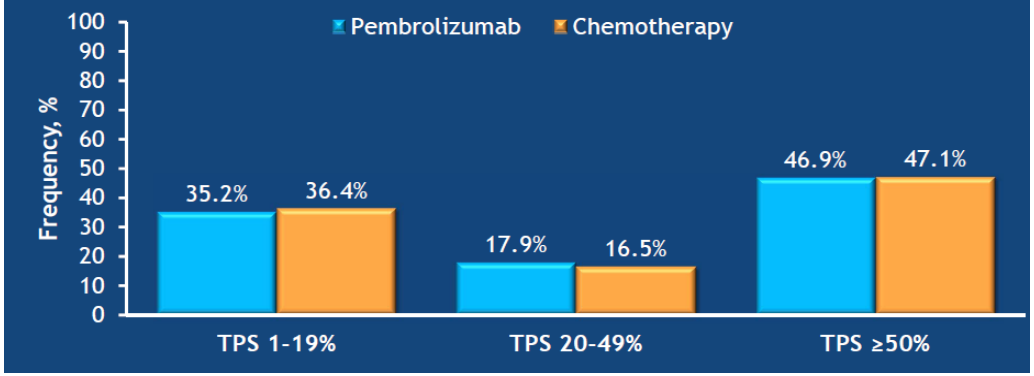
[1]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [2]Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guandong, China; [3]Riga East Clinical University - Latvian Oncology Center, Riga, Latvia; [4]The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [5]Yonsei Cancer Center, Seoul, South Korea; [6]Instanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey; [7]Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; [8]Siriraj Hospital, Bangkok, Thailand; [9]NN Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [11]Nippon Medical School Hospital, Tokyo, Japan;

## KEYNOTE-042 Study Design

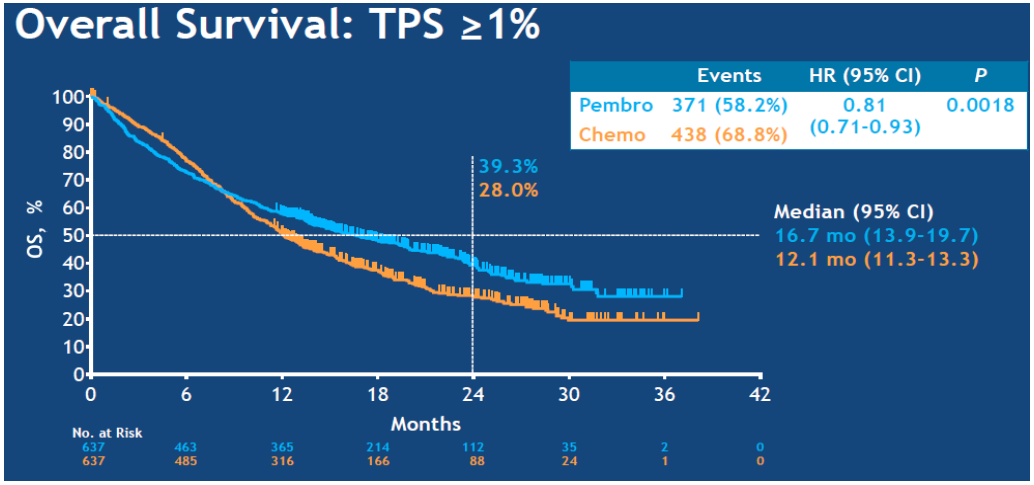



*G Lopes. ASCO 2018. Plenary sesion. Abstract LBA4*

## Frequency of PD-L1 TPS Categories: TPS ≥1% Population




## Overall Survival: TPS ≥1%

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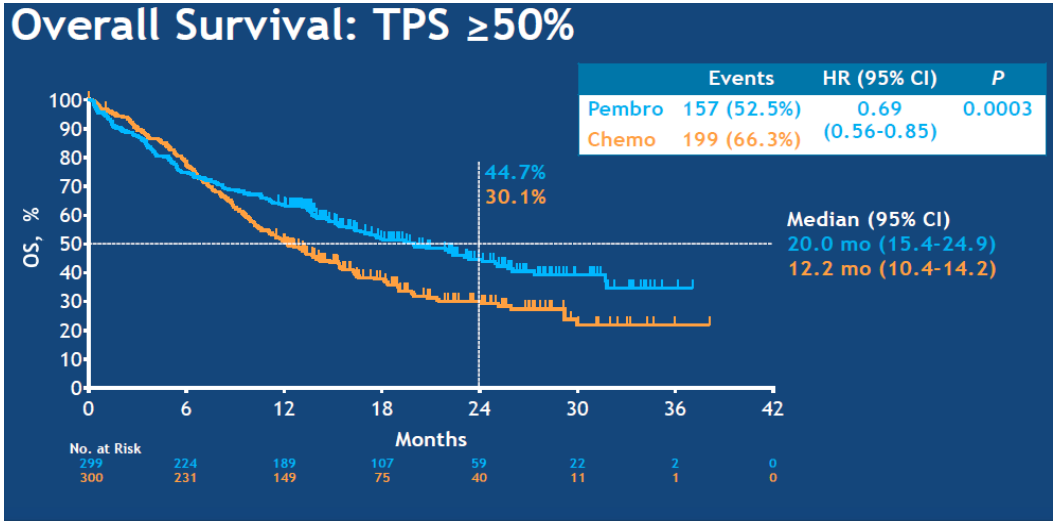
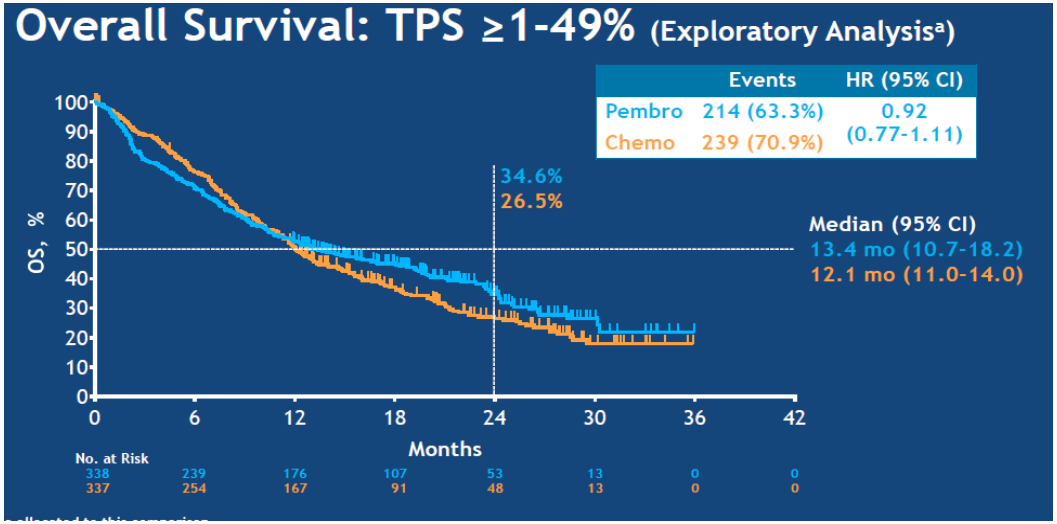
## Overall Survival: TPS ≥50%




## Overall Survival: TPS ≥1-49% (Exploratory Analysis[a])

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